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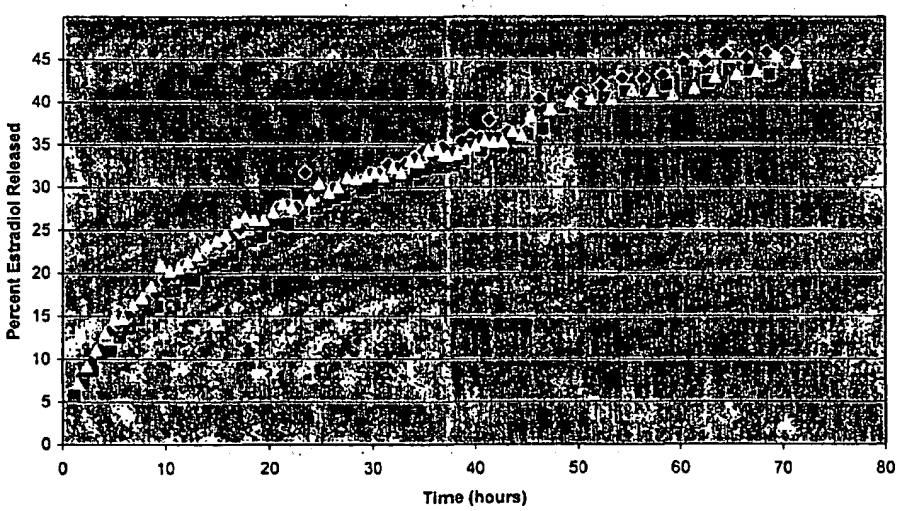
(54) Title: FLUOROPOLYMER COATINGS FOR IMPLANTABLE MEDICAL DEVICES



(57) Abstract: A coating for an implantable medical device is disclosed. The coating comprises a fluorinated polymer soluble in an organic solvent or a mixture of organic solvents. A method for improving barrier properties of coatings for implantable medical devices is also provided.

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FLUOROPOLYMER COATINGS FOR IMPLANTABLE MEDICAL DEVICES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to coatings for drug delivery devices, such as drug eluting vascular stents. More particularly, this invention is directed to coatings for controlling the rate of release of drugs from stents and methods of fabricating the same.

Description of Related Art

In the treatment of vascular disorders, stents have become a standard adjunct to balloon angioplasty. Stents can eliminate vasospasm, tack dissections to the vessel wall, and reduce negative remodeling. In addition to mechanical functionality, stents are being modified to provide pharmaceutical therapy. Local drug delivery with a stent can provide an efficacious concentration of a drug to the treatment site. In contrast, systemic administration of the medication may produce adverse or toxic side effects for the patient. Local delivery of a drug to the patient via a stent can be the preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site.

Stents are typically made from interconnected struts that are usually between 50 and 150 microns wide. Being made of a metal, such as stainless steel, bare stents have to be modified so as to provide a means for drug delivery. Accordingly, stents are being modified by forming a polymeric coating, containing a drug, on the surface of the stent. A polymer dissolved in a solvent and a drug added thereto can be sprayed on the stent or the stent can be immersed in the composition. Once the solvent evaporates from the composition, a polymeric film layer containing a drug remains on the surface of the stent.

To the extent that the mechanical functionality of stents has been optimized, continued improvements can be made to the coating for stents. For example, one improvement can be for maintaining the concentration of a drug at a therapeutically effective level for an acceptable period of time. Accordingly, controlling or, in effect, decreasing the rate of release of a drug from the stent is important in order to provide for long term sustained drug release. One way of controlling the release rate of the drug from a polymer layer is by the deposition of a topcoat layer on the drug-polymer layer. The topcoat layer serves as a barrier membrane, retarding the process of dissipation of the drug. The current topcoat technology can be improved by providing topcoats having low water absorption, high hydrophobicity and increased biological stability and compatibility. In addition, the topcoats can have other important functions, such as providing the stent with increased lubricity.

In light of the foregoing, the embodiments of the present invention provide for coatings for implantable medical devices, such as stents, with improved characteristics for the delivery of pharmaceutical agents.

SUMMARY

According to one embodiment of the present invention, a coating for an implantable medical device is provided, the coating comprises a fluorinated polymer soluble in an organic solvent or a mixture of organic solvents. Examples of the fluorinated polymer include poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropene), poly(tetrafluoroethylene), fluorinated poly(ethylene-co-propylene), poly(hexafluoropropene), poly(chlorotrifluoroethylene), poly(vinylidene fluoride-co-tetrafluoroethylene), poly(tetrafluoroethylene-co-hexafluoropropene), poly(tetrafluoroethylene-co-vinyl alcohol), poly(tetrafluoroethylene-co-vinyl acetate), poly(tetrafluoroethylene-co-propene), poly(hexafluoropropene-co-vinyl alcohol), poly(tetrafluoroethylene-co-fluoromethylvinyl ether), poly(ethylene-co-tetrafluoroethylene), poly(ethylene-co-hexafluoropropene), poly(vinylidene

fluoride-co-chlorotrifluoroethylene), fluorinated silicones, and mixtures thereof. The fluorinated polymer can have a solubility parameter lower than about 11 $(cal/cm^3)^{1/2}$.

According to another embodiment of the present invention, a method for improving barrier properties of a coating for an implantable medical device is provided, the method comprises including into the coating a fluorinated polymer soluble in an organic solvent or a mixture of organic solvents.

According to yet another embodiment of the present invention, a method for coating a stent is provided, the method comprises applying a fluorinated polymer dissolved in an organic solvent to the stent and allowing the organic solvent to evaporate.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1 and 2 illustrate the results of the drug release by coatings fabricated according to some embodiments of the present invention.

FIGs. 3-5 are histology slides showing the results of the biocompatibility studies of coatings fabricated according to some embodiments of the present invention.

DETAILED DESCRIPTION

A stent coating according to the present invention can include an optional primer layer, a drug-polymer layer, a topcoat layer, an optional intermediate membrane, and an optional finishing coat layer. The drug-polymer layer serves as a reservoir for the therapeutic substance. The primer layer can be used if there is a need to improve the adhesion of the stent coating to the bare surface of the stent, particularly when the drug in the coating may compromise the adhesion. Each of these layers can be formed by dissolving a polymer in a suitable solvent to be selected by those having ordinary skill in the art, followed by applying the solution to the stent, for example, by dipping, brushing, spraying, or other conventional coating methods.

A copolymer of ethylene and vinyl alcohol (EVAL) is one example of a polymer that can be used to fabricate the optional primer layer and/or the drug-polymer layer. EVAL has the general formula $-[CH_2-CH_2]_m-[CH_2-CH(OH)]_n-$. EVAL is a product of hydrolysis of ethylene-vinyl acetate copolymers and may also be a terpolymer including up to 5 molar % units derived from styrene, propylene and other suitable unsaturated monomers. A brand of copolymer of ethylene and vinyl alcohol distributed commercially by Aldrich Chemical Co. of Milwaukee, Wisconsin, or manufactured by EVAL Company of America of Lisle, Illinois, can be used.

Alternatively, a block copolymer can be used to fabricate the optional primer layer and/or the drug-polymer layer. The block-copolymer is also called "a segmented copolymer." The term "block copolymer" is defined in accordance with the terminology used by the International Union of Pure and Applied Chemistry (IUPAC) and refers to a copolymer containing a linear arrangement of blocks. The block is defined as a portion of a polymer molecule in which the monomeric units have at least one constitutional or configurational feature absent from the adjacent portions.

For example, a block copolymer of A and B may be written as ...–A–A–A–B–B–B–.... The blocks of "A" and "B" can have the same or different number of units of "A" and "B." The blocks need not be linked on the ends, since the individual blocks are usually long enough to be considered polymers in their own right. The term copolymer is intended to broadly include two or more types of blocks such as tri-blocks.

Examples of block-copolymers that can be used include such classes of block copolymers as polyureas, polyurethanes, polyureaurethanes, for example, BIOMER, styrene-butadiene-styrene tri-block copolymers, styrene-isoprene-styrene tri-block copolymers, and styrene-ethylene/propylene-styrene tri-block copolymers. The polyurethanes that can be used include:

(a) polyurethanes having poly(dimethylsiloxane) soft segments, such as ELAST-EON;

(b) polyurethanes having polycarbonate soft segments, such as BIONATE;

(c) polyurethanes having polyether soft segments, such as PELLETHANE, TECOTHANE or TECOFLEX;

(d) polyurethanes with polyester soft segments; and

(e) polyurethanes with aliphatic soft segment.

BIOMER is a trade name of a poly(ether-urethane-urea) tri-block copolymer and is available from Johnson & Johnson Co. of New Brunswick, New Jersey.

ELAST-EON is a trade name of a product of co-polycondensation of an isocyanate-based component (the hard segment) and a hydrophobic polymeric component (the soft segment) and is available from AorTech Biomaterials Co. of Chatswood, Australia. With respect to one grade of ELAST-EON, the isocyanate-based component can be synthesized by reacting an aromatic diisocyanate, 4,4'-methylene-bisphenyl-diisocyanate (MDI) with butane-1,4-diol. The hydrophobic soft segment can be a blend of poly(hexamethylene glycol) and a carbinol-terminated polydimethylsiloxane (PDMS).

BIONATE is a trade name of a thermoplastic polycarbonate-urethane elastomer formed as the product of the reaction between a hydroxyl-terminated polycarbonate, an aromatic diisocyanate, and a low molecular weight glycol used as a chain extender. BIONATE is available from The Polymer Technology Group Incorporated of Berkeley, California.

PELLETHANE is a trade name of a family of polyether- or polyester-based thermoplastic polyurethane elastomers registered to Upjohn Co. of Kalamazoo, Michigan and available from Dow Chemical Co. of Midland, Michigan.

TECOTHANE is a trade name of a family of aromatic, polyether-based thermoplastic polyurethane elastomers and TECOFLEX – a trade name of family of aliphatic, polyether-based

thermoplastic polyurethane elastomers. Both TECOTHANE and TECOFLEX are available from Thermedics, Inc. of Woburn, Massachusetts.

Alternatively, the optional primer layer can be also fabricated of a silane, a siloxane, an amorphous fluorocarbon solvent-soluble perfluoropolymer, a fluorinated silicone, poly(vinylidene fluoride) (PVDF), a copolymer of poly(tetrafluoroethylene) (PTFE) and fluoromethylvinyl ether, a fluoroalkoxyl-containing polymer, a mixture of silicone and fluoropolymer, or combinations thereof.

Yet another example of a material suitable for making the optional primer layer is a PTFE/silicone copolymer, polymerized on the stent's surface via glow discharge. Still another example of a suitable polymer for fabricating the optional primer layer is a PARYLENE coating. PARYLENE is a trade name of a poly(*para*-xylylene)-based coating available from Specialty Coating Systems, Inc. of Indianapolis, Indiana.

If the adhesion still needs to be improved, a primer layer having more than one sub-layer can be used, e.g. poly(butyl methacrylate) sub-layer may be applied to the bare stent first, followed by application of a fluorine-containing polymer such as PTFE-co-fluoromethylvinyl ether, and finally followed by application of the amorphous PTFE.

Alternatively, other polymers can be used to make the optional primer layer and/or the drug-polymer layer, if desired. Representative examples of such alternative polymers include poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride, polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene halides, such as polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as

polystyrene), polyvinyl esters (such as polyvinyl acetate), copolymers of vinyl monomers with each other and olefins (such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers), polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

The therapeutic substance of drug can include any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. The drug may include small molecule drugs, peptides or proteins. The drug can be for inhibiting abnormal or inappropriate migration and proliferation of smooth muscular cells for the treatment of restenosis.

Examples of the drugs which are usable include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of antineoplastics and/or antimitotics include paclitaxel, docetaxel, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride, and mitomycin. Examples of antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, heparin derivatives containing hydrophobic counter-ions, hirudin, argatroban, forskolin, analogues, vapiprost, prostacyclin and prostacyclin dextran, D- phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin. Examples of cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril, cilazapril or lisinopril, calcium

channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (ω-3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus, clobetasol, dexamethasone and its derivatives, and rapamycin, its derivatives and analogs, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis Corp. of New York), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin.

EVAL can be also used to make the optional finishing coat layer and/or the topcoat layer. However, in some cases, in order to provide a topcoat layer with improved barrier properties, it may be desirable to choose a polymer other than EVAL. Thus, the topcoat layer and the optional finishing coat layer can be fabricated of a polymer having hydrophobicity higher than that of pure EVAL.

Generally, hydrophobicity of a polymer can be gauged using the Hildebrand solubility parameter δ. Hydrophobic polymers typically have a low δ value. A polymer sufficiently hydrophobic to be used in the topcoat layer or the optional finishing coat layer can have a solubility parameter lower than about 11 $(cal/cm^3)^{1/2}$. The term "Hildebrand solubility parameter" refers to a parameter measuring the cohesive energy density of a substance. The δ parameter is determined as follows:

$$\delta = (\Delta E/V)^{1/2}$$

where δ is the solubility parameter, $(cal/cm^3)^{1/2}$; ΔE is the energy of vaporization, cal/mole; and V is the molar volume, cm^3/mole.

Consequently, various embodiments of the present invention described below are directed to the stent coating such that the outermost layer of the coating (i.e., the topcoat layer or the optional finishing coat layer) includes a hydrophobic fluorinated polymer soluble in an organic solvent or a blend of organic solvents. In some embodiments, more particularly in embodiments in which a topcoat layer as well as a finishing coat layer disposed on the topcoat layer is used, both the topcoat layer and finishing coat layer may include a fluorinated polymer. Optionally, the drug-polymer layer can also be made out of the fluorinated polymer, if desired.

Examples of highly fluorinated polymers include PVDF having a general formula $-[CF_2-CH_2]_m-$, and poly(vinylidene fluoride-co-hexafluoropropene) (PVDF-HFP) having a general formula $-[CF_2-CH_2]_m-[CF_2-\underset{\displaystyle CF_3}{\underset{|}{CF}}]_n-$.

A brand of PVDF known under the trade name KYNAR available from Atofina Chemicals, Inc. of Philadelphia, Pennsylvania, can be used.

In the alternative, those having ordinary skill in the art may select other highly fluorinated polymers. For the purposes of the present invention, the term "highly fluorinated polymer" is defined as any homopolymer, copolymer, terpolymer or a blend thereof in which at least 50% of monovalent atoms in the macromolecule are fluorine atoms.

One group of such suitable alternative highly fluorinated polymers includes polymers based on fluorinated olefins or mixtures thereof. The term "polymers based on fluorinated olefins" refers to the polymers which include units derived from fully or partially fluorinated olefins, such as fluorinated ethylene. Examples of some polymers belonging to this group are provided in Table 1.

Table 1. Examples of Olefin-Based Fluorinated Polymers Suitable for Stent Coatings.

No.	Fluorinated Polymer	Abbreviation	General Formula
1	Poly(tetrafluoroethylene) *)	PTFE	$-[CF_2-CF_2]_m-$
2	Fluorinated poly(ethylene-co-propylene)	FPEP	$-[CF_2-CHF]_m-[CH_2-\underset{CF_3}{CH}]_n-$ **)
3	Poly(hexafluoropropene)	PHFP	$-[CF_2-\underset{CF_3}{CF}]_n-$
4	Poly(chlorotrifluoroethylene)	PCTFE	$-[CClF-CF_2]_m-$
5	Poly(vinylidene fluoride)***)	PVDF	$-[CF_2-CH_2]_m-$
6	Poly(vinylidene fluoride-co-tetrafluoroethylene)	PVDF-TFE	$-[CF_2-CH_2]_m-[CF_2-CF_2]_n-$
7	Poly(vinylidene fluoride-co-hexafluoropropene)	PVDF-HFP	$-[CF_2-CH_2]_m-[CF_2-\underset{CF_3}{CF}]_n-$
8	Poly(tetrafluoroethylene-co-hexafluoropropene)	PTFE-HFP	$-[CF_2-CF_2]_m-[CF_2-\underset{CF_3}{CF}]_n-$
9	Poly(tetrafluoroethylene-co-vinyl alcohol)	PTFE-VAL	$-[CF_2-CF_2]_m-[CH_2-\underset{OH}{CH}]_n-$
10	Poly(tetrafluoroethylene-co-vinyl acetate)	PTFE-VAC	$-[CF_2-CF_2]_m-[CH_2-\underset{OC(O)CH_3}{CH}]_n-$
11	Poly(tetrafluoroethylene-co-propene)	PTFEP	$-[CF_2-CF_2]_m-[CH_2-\underset{CH_3}{CH}]_n-$
12	Poly(hexafluoropropene-co-vinyl alcohol)	PHFP-VAL	$-[CF_2-\underset{CF_3}{CF}]_n-[CH_2-\underset{OH}{CH}]_n-$
13	Poly(ethylene-co- tetrafluoroethylene)	PETFE	$-[CH_2-CH_2]_m-[CF_2-CF_2]_n-$
14	Poly(ethylene-co-hexafluoropropene)	PEHFP	$-[CH_2-CH_2]_m-[CF_2-\underset{CF_3}{CF}]_n-$
15	Poly(vinylidene fluoride-co-chlorotrifluoroethylene)	PVDF-CTFE	$-[CF_2-CH_2]_m-[CClF-CF_2]_m-$

*) Including various brands of TEFLON available from E.I. DuPont de Nemours & Co. of Wilmington, Delaware.

**) The formula shows an example of one possible FPEP. Other kinds of FPEP can be used.

***)Including various brands of KYNAR

The fluorinated polymers discussed above are highly hydrophobic. For example, PTFE has a Hildebrand solubility parameter of 6.2. Other highly fluorinated polymers that can be used for making the topcoat layer, the finishing coat layer and/or the drug-polymer layer include polymers having heterocyclic fragments or having oxygen atoms in the backbone. These classes of polymers are not based on fluorinated olefins. Examples of such polymers include:

(1) amorphous products of polymerization of fluorinated cyclic esters, such as poly(perhalo-2,2-di-loweralkyl-1,3-dioxole-co-perfluoro-2-methylene-methyl-1,3-dioxolane) (designated for the purposes of this invention as "polyfluorooxalanes"), for example, poly(perhalo-2,2-dimethyl-1,3-dioxole-co-perfluoro-2-methylene-methyl-1,3-dioxolane);

(2) thermoplastic resinous fluorine-containing cyclic polymers having a main chain with an asymmetrical cyclic structure, with repeating units of cyclically polymerized perfluorallyl vinyl ether and/or perfluorobutenyl vinyl ether, e.g., poly(perfluorobutenyl vinyl ether) (PPBVE); and

(3) copolymers of perfluoro-2,2-dimethyl-1,3-dioxole (PDD) with such monomers as perfluoroolefins and perfluoro(alkyl vinyl) ethers (designated for the purposes of this invention as "polyfluorooxoles"), including the TEFLON AF product. TEFLON AF is a trade name of a product which includes poly(tetrafluoroethylene-co-perfluoro-2,2-dimethyl-1,3-dioxole) and which is available from E.I. DuPont de Nemours & Co.

Polyfluorooxoles can contain between about 1 and 99.5% (molar) units derived from PDD and the balance of units derived from perfluoro(butenyl vinyl ether), and can optionally contain minor amounts of additional monomers, such as chlorinated or fluorinated olefins, e.g., tetrafluoroethylene or chlorotrifluoroethylene, and perfluorvinyl ethers such as perfluoropropylvinyl ether, perfluoro-3,6-dioxa-4-methyl-7-octenesulfonyl fluoride and methyl

perfluoro-4,7-dioxa-5-methyl-8-nonenoate. A PPVBE brand under the trade name CYTOP, available from Asahi Glass Co. of Charlotte, North Carolina, can be used.

All fluorinated polymers used in the present invention are soluble in at least one organic solvent, or a blend of various organic solvents. Suitable solvents include fluorinated solvents, for example, fluorocarbon systems having the boiling temperature of about 60°C to about 140°C, such as FLUORINERT FC-75 and various FREONs, and other fluorinated solvents, such as FLUX REMOVER AMS and NOVEC hydrofluoroether solvents.

FLUORINERT FC-75 is a trade name of perfluoro(2-butyltetrahydrofuran), a solvent which is available from Minnesota Mining and Manufacturing Corp. of Saint Paul, Minnesota. FREON is a trade name of various chlorinated fluorocarbons available from E.I. DuPont de Nemours & Co.

FLUX REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Texas comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and a balance of methanol, with trace amounts of nitromethane. NOVEC is a trade name of a family of solvents based on hydrofuoroethers available from 3M Corp. of St. Paul, Minnesota.

Other solvents can be alternatively used to dissolve the above described fluorinated polymers. Representative examples of such other suitable solvents include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), dimethylsulphoxide (DMSO), acetone, cyclohexanone, methyl isobutyl ketone, methyl ethyl ketone, N-methyl pyrrolidone, and 1,4-dioxane.

To form the topcoat layer, the finishing layer and/or the drug-polymer layer, the layer can be applied from a polymer solution as described above. To prepare the polymer solution, one or a blend of several of the fluoropolymers described above can be dissolved in one or a blend of several of the above-mentioned solvents. If it is desirable to incorporate EVAL or other

non-fluorinated polymers described above into the topcoat layer, the finishing layer and/or the drug-polymer layer, they can be included in the polymer solution. No cross-linking of the coating or exposure of the coating to high temperatures is required for the curing of the coating, but moderate heat can be optionally applied to facilitate the removal of the solvent.

To improve the barrier properties of the topcoat layer even more, in one embodiment, an intermediate membrane can be applied below the topcoat layer, or between the topcoat layer and the finishing layer which is deposited on top of the topcoat layer. The intermediate membrane can be applied by chemical vapor deposition according to techniques known to those skilled in the art. Typical materials used for depositing the intermediate membrane include tetrafluoroethylene and vinylidene fluoride to obtain a PTFE-like or PVDF-like membrane.

Non-fluorinated materials, such as PARYLENE or DYLYN can alternatively be used to make the intermediate membrane. DYLYN is a trade name of a pyrolytic carbon coating having abstractable hydrogen (diamond-like coating having both sp^2 and sp^3 carbon atoms and applied by plasma-assisted chemical vapor deposition). DYLYN can be obtained from ART, Inc. of Buffalo, New York.

The coatings of all the embodiments of the present invention have been described in conjunction with a stent. However, the coatings can also be used with a variety of other medical devices. Examples of the implantable medical devices that can be used in conjunction with the embodiments of this invention, include stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, axius coronary shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt-chromium alloys (e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium

alloy, iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations thereof. Devices made from bioabsorbable or biostable polymers can also be used with the embodiments of the present invention.

"MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

EXAMPLES

Embodiments of the present invention can be further illustrated by the following Examples.

Example 1

A first composition was prepared by mixing the following components:

(a) about 2.0 mass% of EVAL; and

(b) the balance, a mixture of solvents, DMAC and ethanol, in a ratio of DMAC to ethanol of about 70:30 by mass.

The first composition was applied onto the surface of a bare 13 mm TETRA stent (available from Guidant Corp.) by spraying and dried to form a primer layer. A spray coater having an EFD 7803 spray valve with 0.014 inch fan nozzle with a VALVEMATE 7040 control system, manufactured by EFD, Inc. of East Providence, Rhode Island was used. The fan nozzle was maintained at about 60°C with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.35 atm (about 20 psi). An average of about 19 micrograms (μg) per coating pass was applied and an average total of about 62 μg of the wet coating was applied.

The primer layer was baked at about 140°C for about one hour, yielding a layer with an average total amount of solids of about 61 μg, corresponding to an average thickness on the stent of 0.65 μm. "Solids" means the amount of dry residue deposited on the stent after all volatile organic compounds (e.g., the solvent) have been removed.

The second composition was prepared by mixing the following components:

(c) about 2.0 mass% of EVAL

(d) about 0.7 mass % rapamycin; and

(e) the balance, a mixture of solvents, DMAC and ethanol, in a ratio of DMAC to ethanol of about 70:30 by mass.

A second composition was applied onto the dried primer layer to form a drug-polymer layer using the same spraying technique and equipment used for the primer layer. About 497 μg of the wet coating was applied, followed by drying at about 50°C for about 2 hours. The total amount of solids of the drug-polymer layer was about 494 μg, corresponding to an average thickness on the stent of about 5.3 μm.

A third composition was prepared by mixing the following components:

(g) about 2.0 mass % of PVDF-HFP; and

(h) the balance, a mixture of solvents, cyclohexanone, acetone, and AMS FLUX REMOVER in a ratio of 25:50:25 by mass.

The third composition was applied onto the drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and drug-polymer layers. About 475 μg of wet coating was applied, followed by baking at about 50°C for about 2 hours. The average total amount of solids of the topcoat layer was about 449 μg, corresponding to an average thickness on the stent of about 3.08 μm.

The properties of the coating obtained according to the procedure described above are summarized as shown in Table 2.

Table 2. The Properties of the Coating of Example 1.

Layer of the Coating	Weight, μg	Average Thickness, μm
EVAL Primer	61 ± 5	0.65
Rapamycin/EVAL drug-polymer layer	494 ± 21	5.3
PVDF-HFP topcoat layer	449 ± 10	3.08
Overall coating	1,004 ± 36	9.03

Example 2

A primer layer and a drug-polymer layer were formed on a stent as described in Example 1. A topcoat composition was prepared by mixing the following components:

(a) about 2.0 mass % of EVAL; and

(b) the balance, a mixture of solvents, DMAC and pentane, in a ratio of DMAC to pentane of about 80:20 by mass.

The topcoat composition was applied onto the drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and drug-polymer layers. About 348 μg of wet coating was applied, followed by baking at about 50°C for about 2 hours. The average total amount of solids of the topcoat layer was about 295 μg, corresponding to an average thickness on the stent of about 3.16 μm.

Example 3

The stents coated according to Examples 1 and 2 were assayed for total drug content by solvent extraction followed by analysis by HPLC. Six stents were used for each group. The average amount of the drug present based on the gravimetric weight of the drug/polymer layer was about 80% of the theoretical amount.

The stents also were assayed for drug release. Again, six stents were used for each group. The stents were immersed in stirred porcine serum at about 37°C for about 24 hours to simulate an *in vivo* environment. The drug remaining on the stent was assayed using the same total drug content assay. It was found that the three stents with the PVDF-HFP topcoat released an average of about 6.5% of the drug indicating a slow release rate. Similar stents with a 285 μg topcoat membrane layer of EVAL released an average of about 14.7% of the rapamycin in about 24 hours under the same conditions. The comparative results for the two groups are provided in Table 3.

Table 3. Comparative Results of the Drug Release Study

Topcoat Layer of the Stent Coating	Average Theoretical Amount of Rapamycin	Actual Amount of Rapamycin, % of Theoretical Amount	Rapamycin Released in 24 hours, %
PVDF-HFP	127	80.5	6.5
EVAL	128	80.1	14.7

The topcoat thicknesses of the PVDF-HFP in Example 1, and the EVAL in Example 2 are close at 3.08 and 3.16 μm, respectively. As seen from the results presented in Table 2, the fluoropolymer topcoat layer of the stent coating provides a substantial (over 55%) decrease in the drug release rate compared to an EVAL topcoat layer.

Example 4

A first composition was prepared by mixing the following components:

(a) about 2.67 g of a 15 mass % solution of EVAL in DMAC;

(b) about 0.20 g of 17-β-estradiol; and

(c) about 17.13 g of additional DMAC.

The first composition was applied onto a stent, to form a drug-polymer layer. About 323 μg of the wet coating was applied. The total amount of solids of the drug-polymer layer was about 316 μg, corresponding to a thickness of about 3.38 μm.

A second composition was prepared by mixing the following components:

(d) about 6.0 g of a 5 mass % solution of KYNAR-FLEX 2800 in acetone;

(e) about 1.65 g of additional acetone;

(f) about 3.675 g of cyclohexanone; and

(g) about 3.675 g of AMS FLUX REMOVER.

The second composition was applied by spraying using an EFD 7803 spray valve with 0.014 inch fan nozzle to form a topcoat layer followed by drying. The nozzle temperature was at ambient with a feed pressure of about 0.2 atm (3 psi) and an atomization pressure of about 1 atm (15 psi). The dryer temperature was at ambient with a dryer air pressure of about 2.7 atm (40 psi). An average of about 15 μg per coating pass was applied and an average total of about 461 μg of wet coating was applied. This topcoat was baked at about 50°C for about two hours yielding a total amount of solids of about 439 μg, corresponding to a thickness of about 3.0 μm.

Example 5

Three stents coated according to Example 4 were assayed for total drug content by solvent extraction followed by analysis by HPLC. The percent drug present, based on the weight of the drug/polymer layer was 92 ± 1.1%. The three stents were also assayed for drug

release. The stents were immersed in stirred porcine serum at about 37°C for about 24 hours to simulate an *in vivo* environment. It was found that the three stents released an average of about 2.5% of the drug indicating a slow release rate. Similar stents with a 300 μg topcoat layer of EVAL released 100% of the 17-β-estradiol in about 24 hours under the same conditions.

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Example 6

A drug-polymer layer was applied onto a stent as described in Example 1, except 17-β-estradiol was used instead of rapamycin. A topcoat composition was prepared by mixing the following components:

10 (a) about 1.2 g of a 10 mass % solution of KYNAR-FLEX 2800 in acetone;

(b) about 1.89 g of additional acetone;

(c) about 5.94 g of cyclohexanone; and

(d) about 2.97 g of AMS FLUX REMOVER.

The topcoat composition was applied by spraying using an EFD 7803 spray valve with 15 0.014 inch fan nozzle to form a topcoat layer, followed by drying. The nozzle temperature was at ambient with a feed pressure of about 0.2 atm (3 psi) and an atomization pressure of about 1 atm (15 psi). The dryer temperature was at ambient with a dryer air pressure of about 2.7 atm (40 psi). An average of about 5 μg per coating pass was applied and an average total of about 60 μg of wet coating was applied. The topcoat layer was baked at about 50°C for two hours 20 yielding a total amount of solids of about 55 μg, corresponding to a thickness of about 0.38 μm.

Three stents coated according to this example were tested for the drug release rate. The stents were immersed in individual, stirred vessels containing a phosphate-buffered saline solution which included about 1 mass % of sodium dodecyl sulfate. The buffer solution had pH 25 of about 7.4 thermostated at 37°C. The amount of 17-β-estradiol released was determined at

measured intervals of time by HPLC. The percent drug released as a function of time for three stents is shown by FIG. 1. The data demonstrates good reproducibility. There is an initial small burst of drug during the first 20 hours, after which the release rate is approximately linear.

Example 7

A first composition was prepared by mixing the following components:

(a) about 10 g of a 10 mass % solution of EVAL in DMAC;

(b) about 0.8 g of EVEROLIMUS;

(c) about 9.56 g of additional DMAC; and

(d) 4.64 g of pentane.

The first composition was applied onto the surface of a bare 18 mm medium VISION stent using an EFD 780S spray valve with a 0.014 inch nozzle tip and a 0.028 inch round air cap to form a drug-polymer layer, followed by drying. The nozzle temperature was at about 45°C with a feed pressure of about 0.2 atm (3 psi) and an atomization pressure of about 1.3 atm (20 psi). The dryer temperature was 80°C with a dryer air pressure of about 1.3 atm (20 psi). An average of about 30 μg per coating pass was applied and an average total of about 332 μg of wet coating was applied. The drug-polymer layer was baked at about 80°C for about two hours yielding a total amount of solids of about 309 μg, corresponding to a thickness of about 2.1 μm.

A second composition was prepared by mixing the following components:

(e) about 4.0 g of a 10 mass % solution of KYNAR-FLEX 2800 in acetone;

(f) about 1.3 g of additional acetone;

(g) about 9.8 g of cyclohexanone; and

(h) about 4.9 g of AMS FLUX REMOVER.

The second composition was applied by spraying using an EFD 7803 spray valve with 0.014 inch fan nozzle tip and 0.014 inch fan air cap to form a topcoat layer, followed by drying. The nozzle temperature was at ambient with a feed pressure of about 0.2 atm (3 psi) and an

atomization pressure of about 1 atm (15 psi). The dryer temperature was at ambient with a dryer air pressure of about 1.35 atm (20 psi). An average of about 10 μg per coating pass was applied. On one group of stents, an average weight of the wet topcoat layer was about 105 μg. On another group of stents, an average weight of the wet topcoat layer was about 164 μg. The topcoat layers in both cases were baked at about 80°C for about one hour yielding total amount of solids of about 79 and 131 μg, respectively, corresponding to average dry topcoat layer thicknesses of about 0.39 and 0.65 μm, respectively.

Three stents of each group were assayed for *in vitro* drug release. The stents were agitated at 37°C in a buffer solution, and at measured intervals of time each solution was assayed for drug content by HPLC. The fraction of EVEROLIMUS released as a function of time for the six stents (two groups of three stents each) is shown by FIG. 2.

In FIG. 2, curves 1-3 correspond to stents having 0.65 μm thick KYNAR-FLEX 2800 topcoat layer. Curves 4-6 correspond to stents having 0.39 μm thick KYNAR-FLEX 2800 topcoat layer. Curves 7-9 correspond to stents having no topcoat layer. FIG. 2 demonstrates that compared to the stents with no topcoat layers, stents having KYNAR-FLEX 2800 substantially reduce the rate of release of everolimus. Different thicknesses of the KYNAR-FLEX 2800 topcoat layer allow for different controlled release rates of EVEROLIMUS.

Example 8

In order to assess the chronic vascular response, a study was done to compare bare metal (uncoated) stents to stents coated KYNAR-FLEX 2800. Both coated and uncoated stents were implanted for 28 days in the porcine coronary system.

To make the coated stents, a first composition was prepared by mixing the following components:

(a) about 6.0 g of a 10 mass % solution of EVAL in DMAC;

(b) about 6.12 g of additional DMAC; and

(c) about 2.88 g of pentane.

The first composition was applied onto a stent using equipment and technique described in Example 1, to form a primer layer. About 66 μg of the wet coating was applied, followed by baking at about 140°C for one hour. The total amount of solids of the dry primer layer was about 65 μg, corresponding to an average thickness of about 0.7 μm.

A second composition was prepared by mixing the following components:

(d) about 7.94 g of a 6.3 mass % solution of PVDF-HFP in acetone;

(e) about 12.25 g of cyclohexanone; and

(f) about 4.81 g of AMS FLUX REMOVER.

The second composition was applied by spraying using an EFD 7803 spray valve with 0.014 inch fan nozzle tip and 0.014 inch fan air cap to form a topcoat layer, followed by drying. The nozzle temperature was at ambient with a feed pressure of about 0.2 atm (3 psi) and an atomization pressure of about 1 atm (15 psi). The dryer temperature was at about 60°C with a dryer air pressure of about 1.35 atm (20 psi). An average of about 20 μg per coating pass was applied. The number of passes was varied. The topcoat layer was baked at about 60°C for about two hours. For one group of stents, the total amount of solids was about 200 μg, corresponding to average dry topcoat layer thicknesses of about 1.4 μm. For another group of stents, the total amount of solids was about 486 μg, corresponding to average dry topcoat layer thicknesses of about 3.3 μm. The stents of both groups coated as described above were mounted onto 3.0 x 13 mm TETRA catheters and sterilized by electron beam radiation.

Non-atherosclerotic healthy farm pigs of either sex, in the weight range of 30-40 kg were used. Seven animals were used with three stents implanted per animal. Ticlopidine, 500 mg, and Aspirin, 325 mg were administered daily starting one day prior to stent implantation. The coronary vessels were randomized. Nine coated stents having a thickness of the topcoat layer of

about 3.3 μm, six coated stents having a thickness of the topcoat layer of about 1.4 μm, and six bare metal stent (controls) were used. The stents were implanted at a target stent-to-artery ratio of 1.1 to 1 (the diameter of the stents was about 10% bigger than the diameter of the arteries).

Of the seven swine, one animal expired 4 days post surgery. The rest of the animals were sacrificed at a 28 day time point post surgery. The vessels were explanted, preserved in 10% formalin, embedded in methacrylate resin, and stained with hemotoxilin and eosin dye. Histological sections were performed and photomicrographs were prepared. The histology slides are shown by FIG. 3 (for the stent having 1.4 μm-thick PVDF-HFP coating), FIG. 4 (3.3 μm-thick PVDF-HFP coating), and FIG. 5 (control bare stent). Morphometric analysis (microscopic examination) of the histograms was done using computerized planimetry. Vessel injury scoring was performed as described in R.S. Schwartz *et al*, Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model, *Journal of American College of Cardiology*, vol. 19, pp. 267-274 (1992). The average vessel injury scores, percent area stenosis (the ratio between the area of neointima and the area circumscribed by inner elastic lamina), and neointimal thickness over the struts (reflecting the growth of the tissue over the stent struts) are shown in Table 3.

Table 3. A Summary of Experiments on Swine

Treatment	Injury Score*) (the Schwartz method)	NeointimalThickness (mm)	Stenosis, %
Bare Stent, 5 stents averages	1.34 ± 0.36	0.30 ± 0.18	32.6 ± 16.1
1.4 μm PVDF-HFP 5 stents averages	1.13 ± 0.10	0.11 ± 0.04	15.3 ± 4.6
3.3 μm PVDF-HFP 8 stents averages	1.18 ± 0.17	0.16 ± 0.11	23.5 ± 11.6

*) The score of "0" (the lowest) indicates no injury; the score of "3" indicates the highest degree of injury.

The 28 days *in vivo* implantation of PVDF-HFP coated stents were well tolerated in the porcine model. No filling defects, lumenal narrowing, aneurysms or thrombus were noted upon angiographic and morphometric analysis. For all of the stents, the struts were well apposed to the vessel wall. The mean morphometric percent stenosis of the PVDF-HFP coated stents is at least equivalent to that of bare stainless steel, indicating suitable biocompatibility of PVDF-HFP polymer for use as a coronary stent coating.

Example 9

A first composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL;

(b) between about 0.05 mass % and about 1.0 mass %, for example, about 0.7 mass % of actinomycin D (AcD); and

(c) the balance, DMAC solvent.

The first composition can be applied onto a stent, to form a drug-polymer layer with about 40 μg of total solids, with or without the optional primer layer.

A second composition can be prepared by mixing the following components:

(d) between about 0.1 mass % and about 15 mass %, for example, about 1.5 mass % of PVDF; and

(e) the balance, DMAC solvent.

The second composition can be applied onto the dried drug-polymer layer, for example, by spraying or dipping, to form the topcoat layer. The topcoat layer can have, for example, a total solids weight of about 30 μg.

Example 10

A first composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL;

(b) between about 0.05 mass % and about 1.0 mass %, for example, about 0.7 mass % of AcD; and

(c) the balance, DMAC solvent.

The first composition can be applied onto a stent, to form a drug-polymer layer with about 40 μg of total solids, with or without the optional primer layer.

A second composition can be prepared by mixing the following components:

(d) between about 0.1 mass % and about 15 mass %, for example, about 1.5 mass % of PVDF; and

(e) the balance DMAC solvent.

The second composition can be applied onto the dried drug-polymer layer, for example, by spraying or dipping, to form a topcoat layer. The topcoat layer can have, for example, a total solids weight of about 30 μg.

A third composition can be prepared by mixing the following components:

(f) about 2.0 mass % of EVAL; and

(g) the balance, DMAC solvent.

The third composition can be applied onto the dried topcoat layer, to form a finishing layer. The finishing layer can have, for example, a total solids weight of about 30 μg.

Example 11

A first composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL;

(b) between about 0.05 mass % and about 1.0 mass %, for example, about 0.7 mass % of AcD; and

(c) the balance, DMAC solvent.

The first composition can be applied onto a stent, to form a drug-polymer layer with about 40 μg of total solids, with or without the optional primer layer.

A second composition can be prepared by mixing the following components:

(d) between about 0.1 mass % and about 15 mass %, for example, about 1.77 mass % of PVDF-HFP;

(e) between about 0.1 mass % and about 15 mass %, for example, about 3.23 mass % of EVAL; and

(f) the balance, DMAC solvent.

The second composition can be applied onto the dried drug-polymer layer, for example, by spraying or dipping, to form the topcoat layer. The topcoat layer can have, for example, a total solids weight of about 30 μg.

Example 12

A first composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL;

(b) between about 0.05 mass % and about 1.0 mass %, for example, about 0.7 mass % of AcD; and

(c) the balance, DMAC solvent.

The first composition can be applied onto a stent, to form a drug-polymer layer with about 40 μg of total solids, with or without the optional primer layer.

A second composition can be prepared by mixing the following components:

(d) between about 0.1 mass % and about 15 mass %, for example, about 2.99 mass % of PVDF;

(e) between about 0.1 mass % and about 15 mass %, for example, about 1.58 mass % of EVAL; and

(f) the balance, DMAC solvent.

The second composition can be applied onto the dried drug-polymer layer, for example, by spraying or dipping, to form the topcoat layer. The topcoat layer can have, for example, a total solids weight of about 30 μg.

Example 13

A first composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL ;

(b) between about 0.05 mass % and about 1.0 mass %, for example, about 0.7 mass % of AcD; and

(c) the balance, DMAC solvent.

The first composition can be applied onto a stent, to form a drug-polymer layer with about 40 μg of total solids, with or without the optional primer layer. A membrane based on a PTFE-like polymer can be formed on top of the drug-polymer layer by chemical vapor deposition of poly(tetrafluoro ethylene). The method of chemical vapor deposition is known to those having ordinary skill in the art. The membrane can have thickness between about 0.05 μm and about 0.25 μm, for example, about 0.1 μm.

A second composition can be prepared by mixing the following components:

(d) between about 0.1 mass % and about 15 mass %, for example, about 1.5 mass % of PVDF; and

(e) the balance, DMAC solvent.

The second composition can be applied onto the membrane fabricated by chemical vapor deposition as described above, for example, by spraying or dipping, to form the topcoat layer. The topcoat layer can have, for example, a total solids weight of about 30 μg.

Example 14

A first composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of ELAST-EON 55 D; and

(b) the balance, a mixture of solvents, DMAC and FLUX REMOVER AMS, in a ratio of DMAC to FLUX REMOVER AMS of about 50:50 by mass.

ELAST-EON 55 D is one of the polymers of the ELAST-EON family and is a an aromatic polyurethane based on a soft segment containing a carbinol-terminated siloxane.

The first composition can be applied onto the surface of a bare 13 mm TETRA stent by spraying and dried to form a primer layer. An average of between about 9 and 12 μg per coating pass can be applied and an average a total of about 50 μg of the wet coating can be applied. The first composition can be baked at about 100°C for about 1 hour, yielding a primer layer.

A second composition can be prepared by mixing the following components:

(c) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of ELAST-EON 55 D;

(d) between about 0.1 mass % and 2.0 mass %, for example, 0.7 mass % of EVEROLIMUS; and

(e) the balance, a mixture of solvents, DMAC and FLUX REMOVER AMS, in a ratio of DMAC to FLUX REMOVER AMS of about 50:50 by mass.

The second composition is applied on top of the dried primer layer to form the drug-polymer layer. The method of applying of the second composition can be the same as for the first composition. An average of between about 14 and 24 μg per coating pass can be applied. After the second composition is applied, it can be baked at about 60°C for about 2 hours, to yield, for example, between about 294 and 311 μg of the dried drug-polymer layer.

A third composition can be prepared by mixing the following components:

(f) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of PVDF-HFP; and

(g) the balance a mixture of solvents, DMAC and acetone, in a ratio of DMAC to acetone of about 50:50 by mass.

The third composition can be applied onto the dried drug-polymer layer, for example, by spraying or dipping, to form the topcoat layer. An average of between about 16 and 19 μg per coating pass can be applied. After the third composition is applied, it can be baked at about 60°C for about 2 hours, to yield, for example, between about 275 and 300 μg of the dried topcoat layer.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

CLAIMS

WHAT IS CLAIMED IS:

1. A coating for an implantable medical device, the coating comprising a fluorinated polymer soluble in an organic solvent or a mixture of organic solvents.

2. The coating of Claim 1, wherein the device is a stent.

3. The coating of Claim 1, wherein the fluorinated polymer is an olefin-based polymer.

4. The coating of Claim 1, wherein the fluorinated polymer is selected from a group consisting of poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropene), poly(tetrafluoroethylene), fluorinated poly(ethylene-co-propylene), poly(hexafluoropropene), poly(chlorotrifluoroethylene), poly(vinylidene fluoride-co- tetrafluoroethylene), poly(tetrafluoroethylene-co-hexafluoropropene), poly(tetrafluoroethylene-co-vinyl alcohol), poly(tetrafluoroethylene-co-vinyl acetate), poly(tetrafluoroethylene-co-propene), poly(hexafluoropropene-co-vinyl alcohol), poly(tetrafluoroethylene-co-fluoromethylvinyl ether), poly(ethylene-co-tetrafluoroethylene), poly(ethylene-co-hexafluoropropene), poly(vinylidene fluoride-co-chlorotrifluoroethylene), fluorinated silicones, and mixtures thereof.

5. The coating of Claim 1, wherein the fluorinated polymer has a solubility parameter lower than about 11 $(cal/cm^3)^{1/2}$.

6. The coating of Claim 1, wherein the fluorinated polymer includes units derived from fluorinated cyclic esters.

7. The coating of Claim 6, wherein the fluorinated polymer includes poly(perhalo-2,2-dimethyl-1,3-dioxole-co-perfluoro-2-methylene-methyl-1,3-dioxolane), poly(perfluoroolefin-co-perfluoro-2,2-dimethyl-1,3-dioxole), or poly[perfluoro(alkyl vinyl) ether-co-perfluoro-2,2-dimethyl-1,3-dioxole].

8. The coating of Claim 7, wherein poly(perfluoroolefin-co-perfluoro-2,2-dimethyl-1,3-dioxole) is poly(tetrafluoroethylene-co-perfluoro-2,2-dimethyl-1,3-dioxole).

9. The coating of Claim 1, wherein the fluorinated polymer includes units derived from fluorinated vinyl ethers.

10. The coating of Claim 9, wherein the fluorinated polymer is poly(perfluorobutenyl vinyl ether).

11. The coating of Claim 1, wherein the solvent is a fluorinated organic substance or a mixture of fluorinated organic substances.

12. The coating of Claim 1, wherein the solvent has a boiling temperature between about 60°C and 140°C.

13. The coating of Claim 1, wherein the solvent is selected from a group consisting of perfluoro(2-butyltetrahydrofuran) and chlorinated fluorocarbons.

14. The coating of Claim 1, wherein the solvent includes a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane.

15. The coating of Claim 1, wherein the solvent is selected from a group consisting of N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, acetone, cyclohexanone, methyl isobutyl ketone, methyl ethyl ketone, N-methyl pyrrolidone, and 1,4-dioxane, and mixtures thereof.

16. The coating of Claim 1, further including a pyrolytic carbon-based polymer or poly(*para*-xylylene).

17. The coating of Claim 1, further including a therapeutic substance.

18. The coating of Claim 17, wherein the therapeutic substance is rapamycin, derivatives or analogs thereof.

19. The coating of Claim 1, further including a block copolymer.

20. The coating of Claim 19, wherein the block copolymer is selected from a group consisting of polyureas, polyurethanes, polyureaurethanes, styrene-butadiene-styrene tri-block

copolymers, styrene-isoprene-styrene tri-block copolymers, and styrene-ethylene/propylene-styrene tri-block copolymers.

21. A method for improving barrier properties of a coating for an implantable medical device, the method comprising including into the coating a fluorinated polymer soluble in an organic solvent or a mixture of organic solvents.

22. The method of Claim 21, wherein the device is a stent.

23. The method of Claim 21, wherein the fluorinated polymer is an olefin-based polymer.

24. The method of Claim 21, wherein the fluorinated polymer is selected from a group consisting of poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropene), poly(tetrafluoroethylene), fluorinated poly(ethylene-co-propylene), poly(hexafluoropropene), poly(chlorotrifluoroethylene), poly(vinylidene fluoride-co- tetrafluoroethylene), poly(tetrafluoroethylene-co-hexafluoropropene), poly(tetrafluoroethylene-co-vinyl alcohol), poly(tetrafluoroethylene-co-vinyl acetate), poly(tetrafluoroethylene-co-propene), poly(hexafluoropropene-co-vinyl alcohol), poly(tetrafluoroethylene-co-fluoromethylvinyl ether), poly(ethylene-co-tetrafluoroethylene), poly(ethylene-co-hexafluoropropene), poly(vinylidene fluoride-co- chlorotrifluoroethylene), fluorinated silicones, and mixtures thereof.

25. The method of Claim 21, wherein the fluorinated polymer has a solubility parameter lower than about 11 $(cal/cm^3)^{1/2}$.

26. The method of Claim 21, wherein the fluorinated polymer includes units derived from fluorinated cyclic esters.

27. The method of Claim 26, wherein the fluorinated polymer includes poly(perhalo-2,2-dimethyl-1,3-dioxole-co-perfluoro-2-methylene-methyl-1,3-dioxolane), poly(perfluoroolefin-co-perfluoro-2,2-dimethyl-1,3-dioxole), or poly[perfluoro(alkyl vinyl) ether-co-perfluoro-2,2-dimethyl-1,3-dioxole].

28. The method of Claim 27, wherein poly(perfluoroolefin-co-perfluoro-2,2-dimethyl-1,3-dioxole) is poly(tetrafluoroethylene-co-perfluoro-2,2-dimethyl-1,3-dioxole).

29. The method of Claim 21, wherein the fluorinated polymer includes units derived from fluorinated vinyl ethers.

30. The method of Claim 28, wherein the fluorinated polymer is poly(perfluorobutenyl vinyl ether).

31. The method of Claim 21, wherein the solvent is a fluorinated organic substance or a mixture of fluorinated organic substances.

32. The method of Claim 21, wherein the solvent has a boiling temperature between about 60°C and 140°C.

33. The method of Claim 21, wherein the solvent is selected from a group consisting of perfluoro(2-butyltetrahydrofuran) and chlorinated fluorocarbons.

34. The method of Claim 21, wherein the solvent includes a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane.

35. The method of Claim 21, wherein the solvent is selected from a group consisting of N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, acetone, cyclohexanone, methyl isobutyl ketone, methyl ethyl ketone, N-methyl pyrrolidone, and 1,4-dioxane, and mixtures thereof.

36. The method of Claim 21, further comprising including into the coating a pyrolytic carbon-based polymer or poly(*para*-xylylene).

37. A method for coating a stent comprising applying a fluorinated polymer dissolved in an organic solvent to the stent and allowing the organic solvent to evaporate.

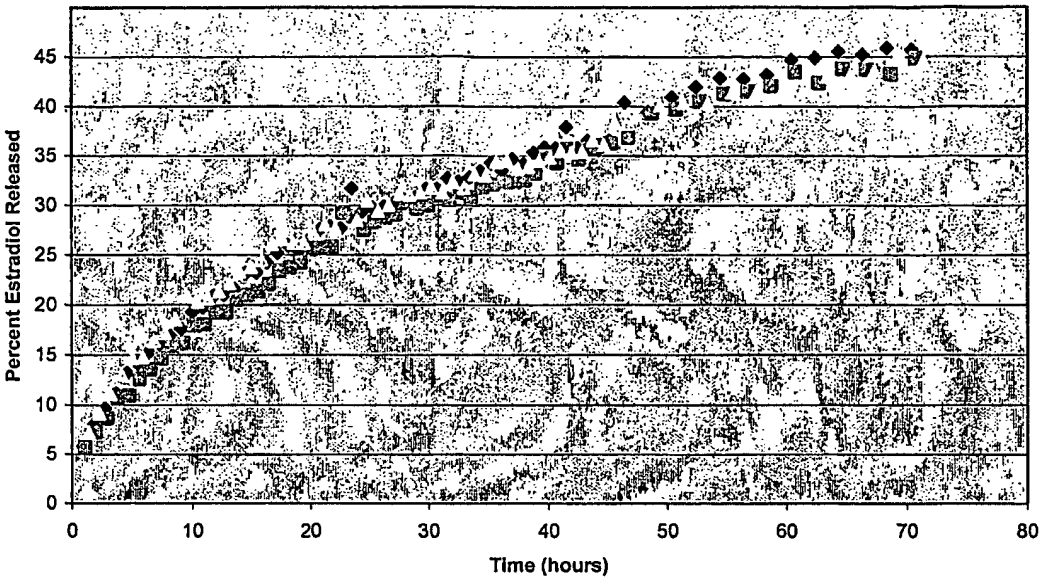
Percent Estradiol Released
0
5
10
15
20
25
30
35
40
45
0
10
20
30
40
50
60
70
80
Time (hours)

Fig. 1

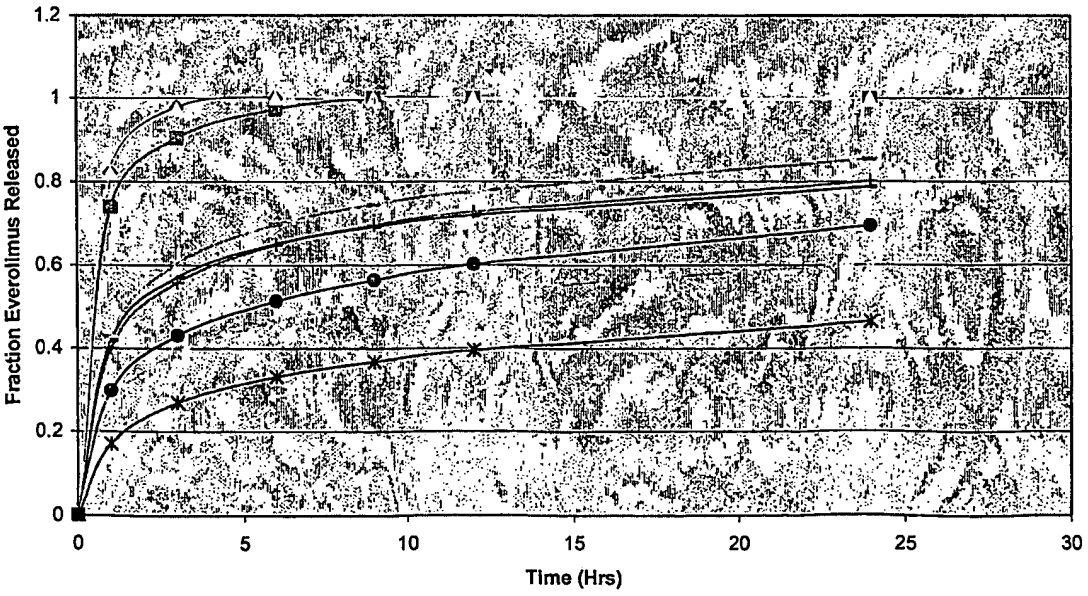
Fraction Everolimus Released
0
0.2
0.4
0.6
0.8
1
1.2
0
5
10
15
20
25
30
Time (Hrs)

Fig. 2

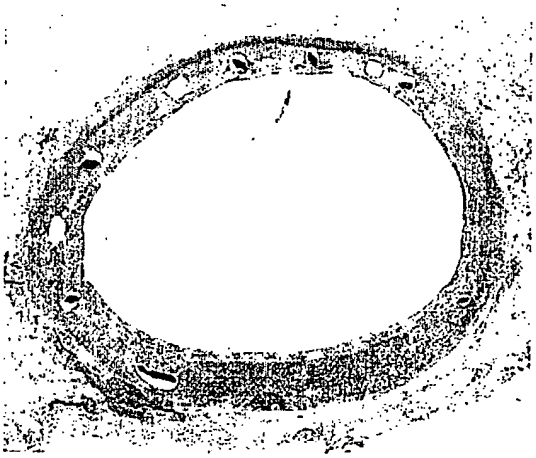

Fig. 3

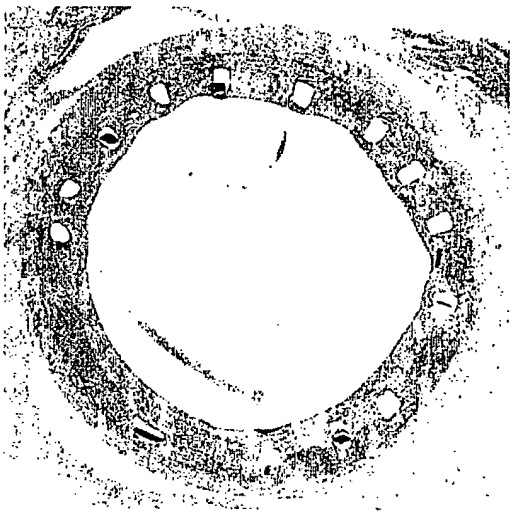

Fig. 4

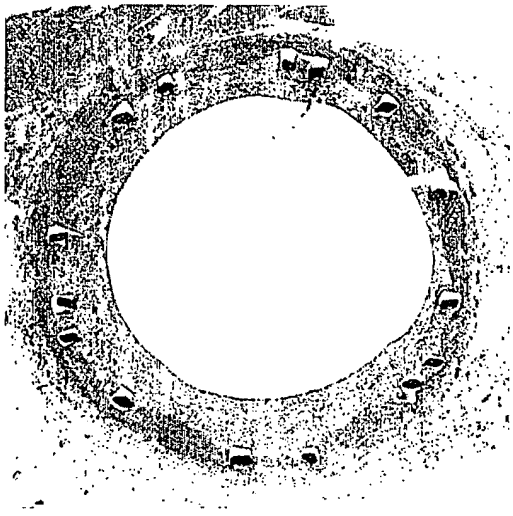

Fig. 5

INTERNATIONAL SEARCH REPORT

Internati cation No
PCT/US 03/28643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/10 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 26271 A (CORDIS CORP) 4 April 2002 (2002-04-04) abstract page 15, line 13 -page 16, line 19 page 25, line 15 -page 26, line 10; examples 1-7 ---	1-37
X	US 6 153 252 A (HOSSAINY SYED F A ET AL) 28 November 2000 (2000-11-28) abstract column 5, line 6 - line 19 column 6, line 43 - line 67 column 7, line 56 -column 8, line 39 ---	1-37
X	US 5 820 917 A (TUCH RONALD J) 13 October 1998 (1998-10-13) abstract column 4, line 59 -column 5, line 22 --- -/--	1-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2003	03/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pilling, S

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INTERNATIONAL SEARCH REPORT

Interna ılication No
PCT/US 03/28643

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 837 008 A (BERG ERIC P ET AL) 17 November 1998 (1998-11-17) abstract column 4, line 43 -column 5, line 3	1-37
X	US 2002/122877 A1 (SANDERS MILLARE DEBORRA ET AL) 5 September 2002 (2002-09-05) abstract paragraph '0025! paragraph '0027! paragraph '0029! - paragraph '0031!	1-37
X	US 5 879 697 A (DING NI ET AL) 9 March 1999 (1999-03-09) abstract column 5, line 38 - line 50 column 7, line 10 - line 15	1-37
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X	US 5 873 904 A (BATES BRIAN L ET AL) 23 February 1999 (1999-02-23) abstract column 13, line 44 - line 53	1-37
X	US 6 299 604 B1 (BATES BRIAN L ET AL) 9 October 2001 (2001-10-09) abstract column 12, line 12 - line 21	1-37
X	WO 01 30403 A (SCIMED LIFE SYSTEMS INC) 3 May 2001 (2001-05-03) page 3, line 26 -page 4, line 32	1-37
X	WO 01 87368 A (ORTHO MCNEIL PHARM INC) 22 November 2001 (2001-11-22) page 7, line 12 -page 8, line 5 page 10, line 16 - line 27	1-37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-37 (part)

Present Claim 1 is directed towards "a coating for an implantable medical device, the coating comprising a fluoronated polymer soluble in an organic solvent or mixture of organic solvents..Etc". Since, the medical device does not clearly appear to be an essential feature of this claim, it appears that Claim 1 is directed towards a group of polymers per se including such well known polymers as PVDF (polyvinylidene fluoride) and PTFE (polytetrafluoroethylene). The initial phase of the search revealed a very large number of documents relevant to the issue of novelty in respect of this claim

It is further noted that there is limited support (Article 6 PCT) for the present claims in the description since the present claims broadly relate to almost any fluorinated polymer/medical device whereas the present description only exemplifies stents coated with PVDF.

For the above reasons a meaningful search over the whole breadth of the claims is impossible and the search was restricted to coatings for stents comprising PVDF. Even this more restricted search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). The Applicant is warned that the presently cited documents are merely a random sample of the many relevant documents found and that it is likely that further searching will be required at a later stage.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/28643

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-37 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internati ication No
PCT/US 03/28643

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